

# Sociodemographic indicators and risk of brain tumours

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**Background** To better understand patterns of occurrence or diagnosis of brain tumours in different segments of the population, we evaluated associations between socio-demographic variables and the relative incidence of brain tumours as part of a multi-faceted case-control study.

**Methods** The study was conducted at hospitals in three US cities between 1994 and 1998. In all, 489 glioma cases (354 high-grade, 135 low-grade), 197 meningioma cases, 96 acoustic neuroma cases, and 799 controls admitted to the same hospitals for any of a variety of non-neoplastic diseases or conditions were enrolled and interviewed. Logistic regression was used to estimate odds ratios (OR), calculate 95% CI, and test for trends.

**Results** The OR showed significant positive associations with household income for low-grade glioma, meningioma, and acoustic neuroma, but not for high-grade glioma. Positive associations were observed with level of education for low-grade glioma and acoustic neuroma, but not for high-grade glioma or meningioma. Jewish religion was associated with a significantly elevated risk for meningioma (OR = 4.3; 95% CI: 2.0–9.0). Being single at the time of tumour diagnosis or enrolment was associated with significantly reduced risks for meningioma (OR = 0.4; 95% CI: 0.3–0.6) and low- or high-grade glioma (OR = 0.6; 95% CI: 0.5–0.8), but not for acoustic neuroma.

**Conclusions** Associations with sociodemographic variables varied considerably among the different subtypes of brain tumour, including between low-grade and high-grade glioma. The general pattern was for associations with indicators of affluence and education to be stronger for tumours that tend to grow more slowly and have less catastrophic effects, although the evidence was mixed for meningioma. We cannot isolate the specific factors underlying the observed associations, but intrapopulation differences in the completeness or timing of diagnosis may have played a role. There is less opportunity for such influences to operate for the rapidly progressing, high-grade gliomas than for more slowly growing tumours.

**Keywords** Brain cancer, brain tumours, social class, glioma, meningioma, acoustic neuroma, epidemiology

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There are few well-established causes of intracranial tumours of the brain and nervous system among adults,<sup>1–3</sup> and investigators have looked to associations between incidence and sociodemographic variables for clues to aetiology. Data show a male predominance of glioma and a substantial female predominance of meningioma.<sup>4–6</sup> The incidences of glioma and acoustic neuroma

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are highest among whites, whereas the incidence of meningioma is highest among blacks.<sup>6</sup> Glioma and acoustic neuroma have been reported to occur more commonly, and meningioma less commonly, among people of higher social class.<sup>4,6–10</sup>

An issue that complicates interpretation of these patterns is the possibility that brain tumours continue to go underdiagnosed in certain segments of the population, even in this era of advanced imaging technology, medical specialization, and improved access to medical care. It is generally believed that the substantial increases in the recorded incidence of brain cancer that occurred among the elderly in the US and other developed countries over the past several decades reflect improvements in the diagnosis of brain tumours rather than a true, large-scale epidemic.<sup>11–15</sup> If underdiagnosis persists, the potential continues to exist for confusing predictors of brain tumour diagnosis with factors related to aetiology.<sup>16</sup> Furthermore, opportunities for early treatment might be missed.

As part of a comprehensive case-control study of malignant and benign brain tumours, we examined associations between sociodemographic variables and the incidence of high- and low-grade glioma, meningioma, and acoustic neuroma. These tumours vary markedly in degree of malignancy, natural history, and clinical presentation; glioblastoma and other high-grade gliomas tend to produce more severe and rapidly progressive symptoms, whereas low-grade gliomas, meningiomas, and acoustic neuromas typically produce less severe, intermittent or slowly progressive symptoms.<sup>17</sup> A comparison of associations for the different tumour types might provide insight into the relative roles of intrapopulation differences in risk, versus diagnosis, of disease.

## Methods

A case-control study of intracranial tumours of the brain and nervous system in adults (age  $\geq 18$  years) was conducted between June 1994 and August 1998 at three hospitals in the US: St Joseph's Hospital and Medical Center in Phoenix, Arizona; Brigham and Women's Hospital in Boston, Massachusetts; and Western Pennsylvania Hospital in Pittsburgh, Pennsylvania. Study participants had to reside within 50 miles of one of the hospitals, or within Arizona for the Phoenix centre, and be able to understand English or Spanish. The study protocol was approved by institutional review boards at the National Cancer Institute and each of the participating hospitals.

Cases were diagnosed with an intracranial glioma or other neuroepitheliomatous tumour, meningioma, or acoustic neuroma (ICD-O-2: 9380–9473 and 9490–9506, 9530–9538, 9560<sup>18</sup>) at one of the three hospitals or during the 8 weeks preceding admission. Microscopic confirmation was required for glioma and meningioma, whereas diagnosis based on magnetic resonance imaging (MRI) was sufficient for acoustic neuroma. All but four acoustic neuromas were microscopically confirmed. Hereafter, the term 'brain tumours' is used to refer to all tumour types, even though neuromas are tumours of the peripheral nervous system. For the present analysis, glioblastoma, gliosarcoma, other anaplastic gliomas (grade III or IV on a four-point scale), and embryonal tumours (medulloblastoma, primitive neuroectodermal tumour, neuroblastoma, astroblastoma) were classified as 'high-grade' and other gliomas as 'low-grade'.<sup>17,19</sup> Tumour histology was ascertained from pathology reports. Information

about duration of tumour-related symptoms at the time of presentation was obtained from hospital charts. Ninety-two per cent of eligible cases (or their proxies) who were asked to participate in the study agreed to do so. The median interval from qualifying diagnosis to enrolment in the study was one week. The case series includes 489 newly diagnosed cases of glioma (354 high-grade, 135 low-grade), 197 cases of meningioma, and 96 cases of acoustic neuroma, or a total of 782 of all tumour types combined.

Hospital controls were frequency-matched to the total case series, based on hospital, age (10-year intervals), sex, race/ethnicity, and distance of residence from hospital (four strata from zero to 50 miles, with a fifth stratum, remainder of state, for the Arizona facility only). The participation rate was 86% among potentially eligible controls who were targeted for enrolment. The 799 controls included 197 (25%) patients admitted because of injuries, 179 (22%) because of diseases of the circulatory system, 172 (22%) because of musculoskeletal diseases, 92 (12%) because of diseases of the digestive system, 58 (7%) with diseases of the nervous system, and 101 (13%) with miscellaneous other conditions.

Study participants, or their proxies, were interviewed in the hospital by a research nurse. The interview included questions about education, household income, type of health insurance, religion, marital status, place of birth, cranial radiotherapy, and other topics not addressed here.<sup>20</sup> Death or incapacitation of the study subject necessitated proxy interviews for 16%, 7%, and 3% of glioma, meningioma, and acoustic neuroma cases, respectively, and 3% of controls. We also ascertained the 1990 median household income for the US Census block corresponding to each person's address at the time of enrolment in the study.

Both unconditional and conditional logistic regression were used to estimate odds ratios (OR), compute associated 95% CI and likelihood ratio statistics, and test for trend or heterogeneity.<sup>21–23</sup> They yielded similar results, and those based on the unconditional analyses are presented here. Analyses were adjusted for matching variables and other covariates, as indicated in the Tables and text. Reference categories were chosen based on distributions among controls. Fisher's exact test was used to test for association in simple  $2 \times 2$  tables. *P*-values are two-sided.

## Results

### Characteristics of cases and controls

Distributions of cases and controls with respect to matching variables are shown in Table 1. The average age at diagnosis was 52 years for glioma, 55 years for meningioma, and 52 years for acoustic neuroma, and the average age at hospital admission was 50 years for controls. Low-grade gliomas tended to be diagnosed at younger ages (mean, 38 years) than high-grade gliomas (mean, 57 years), and most of the gliomas diagnosed past the age of 45 were glioblastoma or anaplastic astrocytoma (Figure 1). The most common types of low-grade glioma were oligodendroglioma, astrocytoma, ganglioglioma, and mixed glioma (Figure 1; Table 1). Astroglial, oligodendroglial, and mixed gliomas together accounted for 91% of the 475 gliomas of specified type. The male to female ratio among cases was 1.3 for glioma, 0.3 for meningioma, and 0.6 for acoustic neuroma; the

**Table 1** Distribution of cases and controls with respect to matching variables

Characteristic	No. (%)		Meningioma (N = 197)	Acoustic neuroma (N = 96)	Controls (N = 799)
	Glioma <sup>a</sup> High-grade (N = 354)	Low-grade (N = 135)			
<b>City/hospital</b>					
Phoenix	168 (47)	76 (56)	99 (50)	72 (75)	405 (51)
Boston	103 (29)	50 (37)	79 (40)	22 (23)	220 (27)
Pittsburgh	83 (23)	9 (7)	19 (10)	2 (2)	174 (22)
<b>Age at diagnosis (years)</b>					
18–24	8 (2)	14 (10)	0 (0)	1 (1)	47 (6)
25–34	24 (7)	44 (33)	16 (8)	9 (9)	118 (15)
35–44	42 (12)	41 (30)	31 (16)	24 (25)	152 (19)
45–54	72 (20)	23 (17)	52 (26)	21 (22)	180 (23)
55–64	76 (21)	6 (4)	39 (20)	21 (22)	122 (15)
65–74	94 (27)	5 (4)	40 (20)	18 (19)	118 (15)
≥75	38 (11)	2 (1)	19 (10)	2 (2)	62 (8)
<b>Sex</b>					
Female	144 (41)	68 (50)	151 (77)	60 (63)	436 (55)
Male	210 (59)	67 (50)	46 (23)	36 (37)	363 (45)
<b>Race/ethnicity</b>					
White, non-Hispanic	324 (92)	120 (89)	163 (83)	89 (93)	715 (89)
White, Hispanic	17 (5)	9 (7)	14 (7)	6 (6)	54 (7)
Black	6 (2)	4 (3)	9 (5)	0 (0)	19 (2)
Asian	4 (1)	0 (0)	4 (2)	1 (1)	1 (0)
American Indian	1 (<1)	1 (<1)	2 (1)	0 (0)	6 (1)
Other/unknown	2 (<1)	1 (<1)	5 (3)	0 (0)	4 (1)
<b>Distance from residence to hospital (miles)<sup>b</sup></b>					
0–5	96 (27)	29 (21)	59 (30)	22 (23)	262 (33)
>5–15	110 (31)	45 (33)	56 (28)	30 (31)	229 (29)
>15–30	81 (23)	35 (26)	43 (22)	17 (18)	163 (20)
>30–50	28 (8)	14 (10)	17 (9)	3 (3)	59 (7)
>50	39 (11)	12 (9)	22 (11)	24 (25)	86 (11)

<sup>a</sup> The high-grade glioma cases (N = 354) include 241 patients diagnosed with glioblastoma (236) or gliosarcoma (5), 70 with anaplastic astrocytoma, 25 with anaplastic oligodendroglioma or anaplastic mixed glioma, 9 with embryonal tumours, and 9 others. The low-grade gliomas (N = 135) include 46 oligodendrogliomas, 34 astrocytomas, 17 gangliogliomas, 14 mixed gliomas, 7 ependymomas, 4 neurocytomas, and 13 others.

<sup>b</sup> Patients residing more than 50 miles from the hospital were eligible only in Phoenix. Distance categories for the hospital in Phoenix were: 0–5, >5–15, >15–35, >35 to 50, and >50 miles (but within Arizona).

sex ratio was 1.0 for low-grade glioma and 1.5 for high-grade glioma ( $P = 0.05$ ). The median duration of tumour-related symptoms prior to histological diagnosis was 1 month for high-grade glioma (mean, 1.9 months), 1 month for low-grade glioma (mean, 11.6 months), 2 months for meningioma (mean, 7.6 months), and 6 months for acoustic neuroma (mean, 13.4 months). Because associations with several demographic variables differed for low- and high-grade glioma, results are presented separately and for all gliomas combined.

### Associations with education, income, and type of health insurance

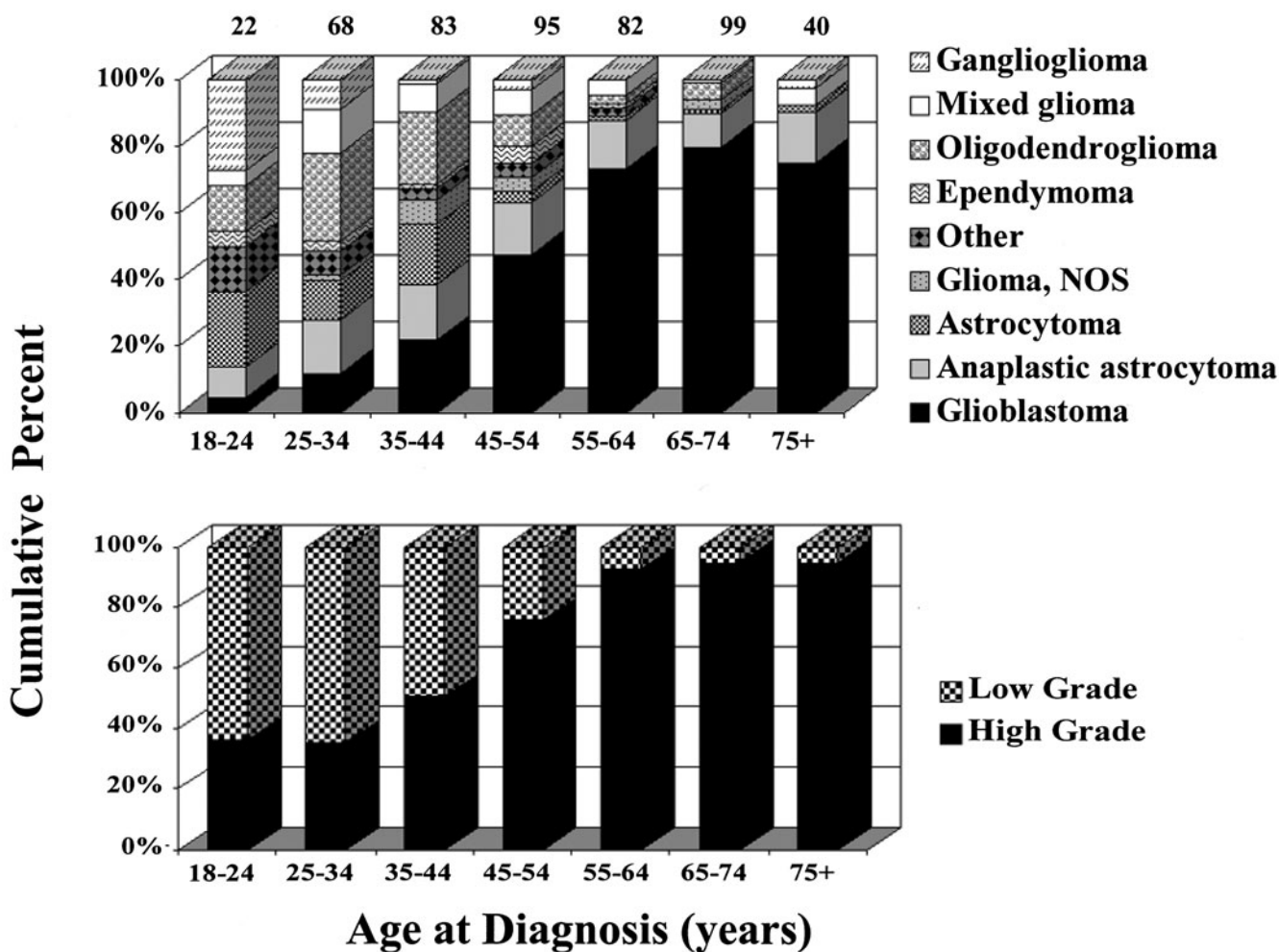
The OR increased with increasing level of education for low-grade glioma and acoustic neuroma, but not for high-grade glioma or meningioma (Table 2). Acoustic neuroma, in particular, was relatively more common among those with ≥4 years of college education. The OR for all tumour types other than high-grade glioma were positively associated with self-reported household income and median household income for census tract of residence. Associations were influenced strongly by low OR for the lowest categories of self-reported income. The OR for acoustic neuroma was particularly high for median household income ≥\$75 000. The two income measures demonstrated only moderate correlation ( $r = 0.38$ ). Associations with education

and income were similar for men and women (data not shown). The associations with education and income did not change substantially with exclusion of any of the major diagnostic subgroups of the control series, as defined above (data not shown). Reported duration of tumour-related symptoms prior to diagnosis was not associated with education or self-reported income.

Most cases and controls had private, fee-for-service health insurance or were covered through a health maintenance organization (HMO) or other prepaid health plan, and there was little difference in OR for these two categories (Table 2). The relative incidence of brain tumours was low among the small number of people covered through Medicaid (a government programme that provides health services to the poor) or not covered at all.

### Marital status

With adjustment for education and self-reported income, OR for meningioma and glioma were higher for people who were married at the time of tumour diagnosis (or enrolment in the study) than for those who were not married, whether widowed, divorced, separated, or never married (Table 3). Contrasting all those currently single with people currently married, the OR were 0.6 for glioma (95% CI: 0.5–0.8) (0.7 for high-grade and



**Figure 1** Histology and grade of glioma cases, by age at diagnosis. In the upper panel, specific histological subtypes occurring in each age interval are shown from top to bottom in the same order as in the key at the right

0.6 for low-grade), 0.4 for meningioma (95% CI: 0.3–0.6), and 1.0 for acoustic neuroma (95% CI: 0.6–1.7). Associations were little influenced by adjustment for type of health coverage and were similar for men and women (data not shown). For glioma, the OR was identical (0.5) for age at diagnosis 40–59 years and age at diagnosis  $\geq 60$  years, but a reduced risk was not seen for the age category 18–39 years (OR = 1.1); ages when tumour symptoms are more likely to be headache or seizures than to involve mental status changes.

#### Religion and place of birth

For all tumour types, the OR was similar for Protestants and Catholics, but it was significantly higher among Jews for meningioma and non-significantly so for acoustic neuroma and glioma (Table 3). These estimates are adjusted for education and household income.

The OR for high-grade glioma and meningioma, but not low-grade glioma or acoustic neuroma, were higher among people who were born outside of the US (Table 3). The positive associations with foreign birth persisted after adjustment for Jewish religion and were most pronounced for the Phoenix centre. Cases in the foreign-born category came from a wide range of countries (Table 3).

#### Discussion

Results indicate considerable heterogeneity in associations between sociodemographic variables and risk of different subtypes of tumours of the brain and nervous system. This heterogeneity goes beyond that described previously for glioma, meningioma, and neuroma,<sup>6</sup> and extends to subsets of glioma. For example, significant positive associations with education and income were seen for low-grade glioma, but not for high-grade glioma, which was more common. This finding parallels the observation of Barker *et al.*<sup>5</sup> that, while the distribution of cases of high-grade astrocytoma by categories of social class in southern England was similar to the social-class distribution for the regional population as a whole, cases of low-grade astrocytoma and oligodendroglioma were over-represented in the higher social classes and under-represented in the lower classes relative to the population distribution. Overall, the general pattern in our study was for associations with indicators of affluence and education to be stronger for tumours that tend to grow more slowly and have less-catastrophic effects.

Slowly growing brain tumours can be present for many years prior to diagnosis, with mild, intermittent, or slowly-progressive symptoms.<sup>17,24–28</sup> Meningiomas and acoustic neuroma, in

**Table 2** Odds ratios (OR) and 95% CI for risk of intracranial tumors of the nervous system, with respect to level of education, self-reported annual household income, median 1990 household income for the census block of residence at the time of diagnosis, and type of health coverage

Characteristic	Glioma											Controls
	All glioma		High-grade		Low-grade		Meningioma		Acoustic neuroma			
	N	OR <sup>a</sup> (CI)	N	OR <sup>a</sup> (CI)	N	OR (CI)	N	OR <sup>a</sup> (CI)	N	OR <sup>a</sup> (CI)		
Highest education level												
<high school	64	1.1 (0.8–1.7)	53	1.4 (0.9–2.1)	11	0.7 (0.3–1.5)	24	0.7 (0.4–1.2)	5	0.6 (0.2–1.5)	105	
High school/GED	122	0.9 (0.7–1.3)	103	1.2 (0.8–1.7)	19	0.4 (0.2–0.7)	57	0.9 (0.6–1.4)	28	1.6 (0.9–3.1)	234	
1–3 years college <sup>b</sup>	130	1.0	84	1.0	46	1.0	68	1.0	21	1.0	245	
4-year college	89	1.5 (1.0–2.1)	60	1.6 (1.1–2.5)	29	1.2 (0.7–2.1)	23	1.0 (0.5–1.7)	23	3.4 (1.7–6.7)	105	
Graduate/professional	68	1.4 (0.9–2.0)	45	1.3 (0.8–2.1)	23	1.8 (1.0–3.4)	24	0.9 (0.5–1.6)	18	3.2 (1.5–6.7)	89	
	<i>P</i> (trend) = 0.04		<i>P</i> (trend) = 0.49		<i>P</i> (trend) = 0.0003		<i>P</i> (trend) = 0.41		<i>P</i> (trend) = 0.001			
Self-reported household income (\$1000s)												
<15	44	0.5 (0.3–0.8)	35	0.5 (0.3–0.8)	9	0.5 (0.2–1.2)	16	0.3 (0.1–0.6)	2	0.1 (0.0–0.5)	125	
15.0–24.9	73	0.9 (0.6–1.4)	56	0.8 (0.5–1.3)	17	0.9 (0.4–2.0)	32	0.9 (0.5–1.6)	10	0.7 (0.3–1.9)	115	
25.0–34.9 <sup>b</sup>	69	1.0	54	1.0	15	1.0	30	1.0	12	1.0	105	
35.0–49.9	84	0.9 (0.6–1.4)	57	0.7 (0.4–1.2)	27	1.3 (0.6–2.8)	31	0.7 (0.4–1.3)	26	1.7 (0.8–3.9)	134	
50.0–74.9	79	0.8 (0.5–1.2)	53	0.6 (0.4–1.0)	26	1.3 (0.6–2.8)	32	0.8 (0.4–1.4)	16	1.0 (0.5–2.5)	145	
≥75.0	102	1.2 (0.8–1.9)	68	1.0 (0.6–1.6)	34	1.8 (0.9–3.7)	39	1.0 (0.6–1.9)	25	2.1 (0.9–4.8)	124	
	<i>P</i> (trend) = 0.02		<i>P</i> (trend) = 0.20		<i>P</i> (trend) = 0.006		<i>P</i> (trend) = 0.01		<i>P</i> (trend) = 0.0001			
Median 1990 household income for census block/tract (\$1000s)												
<15	8	0.4 (0.2–0.8)	6	0.4 (0.2–1.1)	2	0.4 (0.1–1.4)	8	0.9 (0.3–2.1)	3	1.3 (0.3–4.6)	34	
15.0–24.9	97	0.8 (0.6–1.1)	78	0.9 (0.6–1.3)	19	0.6 (0.3–1.1)	30	0.7 (0.4–1.1)	17	1.0 (0.5–2.1)	203	
25.0–34.9 <sup>b</sup>	134	1.0	95	1.0	39	1.0	48	1.0	17	1.0	221	
35.0–49.9	159	1.3 (0.9–1.7)	116	1.3 (0.9–1.9)	43	1.1 (0.7–1.9)	69	1.2 (0.8–2.0)	32	2.1 (1.1–4.2)	210	
50.0–74.9	71	1.0 (0.7–1.5)	46	0.9 (0.6–1.5)	25	1.3 (0.7–2.5)	30	1.3 (0.7–2.2)	17	2.8 (1.3–6.3)	107	
≥75	18	1.3 (0.6–2.6)	11	1.1 (0.5–2.4)	7	1.9 (0.7–5.3)	11	2.3 (0.9–5.3)	9	7.2 (2.5–20)	22	
	<i>P</i> (trend) = 0.01		<i>P</i> (trend) = 0.11		<i>P</i> (trend) = 0.006		<i>P</i> (trend) = 0.009		<i>P</i> (trend) = 0.0001			
Type of medical insurance												
Private <sup>b</sup>	227	1.0	147	1.0	80	1.0	95	1.0	60	1.0	375	
HMO <sup>c</sup>	127	1.0 (0.8–1.4)	88	1.1 (0.7–1.5)	39	1.1 (0.6–1.8)	53	0.9 (0.6–1.4)	23	1.3 (0.7–2.4)	204	
Medicare <sup>d</sup>	109	0.9 (0.6–1.4)	101	0.9 (0.6–1.4)	8	1.1 (0.4–2.7)	41	0.7 (0.4–1.3)	13	0.5 (0.2–1.2)	146	
Medicaid <sup>e</sup>	8	0.5 (0.2–1.1)	4	0.4 (0.4–1.2)	4	0.5 (0.2–1.5)	5	0.7 (0.2–1.7)	0	0.0 (0.0–0.5)	28	
Other	12	0.8 (0.4–1.7)	10	1.2 (0.5–2.6)	2	0.4 (0.1–1.4)	2	0.4 (0.1–1.5)	0	0.0 (0.0–2.0)	23	
None	6	0.5 (0.2–1.1)	4	0.6 (0.2–1.7)	2	0.3 (0.1–1.2)	1	0.2 (0.0–1.2)	0	0.0 (0.0–0.6)	23	

<sup>a</sup> Adjusted for matching variables. The OR for household income measures also are adjusted for date of interview.

<sup>b</sup> Reference category.

<sup>c</sup> Health maintenance organization or other prepaid health plan.

<sup>d</sup> Medicare is a government programme that provides health insurance to people aged ≥65 in the US.

<sup>e</sup> Medicaid is a government programme that provides health coverage for poor people in the US.

particular, often are asymptomatic, or minimally symptomatic, and detected incidentally, either in the course of diagnostic examinations for unrelated reasons or at autopsy in regions with high autopsy rates.<sup>17,29–32</sup> Gliomas encompass a broad spectrum of malignancy and can evolve from less malignant to more malignant forms.<sup>17,33–40</sup> The symptoms associated with glioblastoma and other high-grade gliomas typically are dramatic and rapidly progressive,<sup>17</sup> and it is probable that a high proportion come to diagnosis fairly quickly once they become symptomatic. Low-grade gliomas, on the other hand, follow a more variable and sometimes extended course.<sup>17,25–28,32</sup> Although less likely to go undiagnosed than meningioma, and not commonly first-detected at autopsy, asymptomatic or minimally symptomatic low-grade glioma may be more common at younger ages than previously thought. An MRI survey of 1000 ‘asymptomatic’ people (median age, 29 years) revealed two definite low-grade gliomas and a possible or probable third (prevalence 0.2–0.3%).<sup>32</sup>

For slow-growing tumours, an individual’s response to symptoms and access to medical specialists and diagnostic technology could influence the probability or timing of diagnosis. A long delay in diagnosis would allow time for evolution to a

higher-grade variant, death due to an undiagnosed brain tumour, or death due to an unrelated cause. Determinants of delay in cancer diagnosis have been evaluated more thoroughly for other types of cancer than for brain tumours, but include factors associated with the patient, his or her family and physician, and the medical care system.<sup>41–48</sup> Education and income might influence the awareness or recognition of symptoms and potential benefits of care, and the ability to afford such care.<sup>41,45,49</sup> Positive geographical correlations have been noted between brain tumour occurrence and the per capita number of physicians, specialists, and hospital beds,<sup>50,51</sup> which suggests the importance of availability of medical care. People lacking health insurance or covered through Medicaid were at reduced risk of being diagnosed with a brain tumour in the present study, and previous studies of other types of cancer have shown that such people tend to have their cancers diagnosed at a more advanced stage.<sup>52</sup> A positive association between brain tumour risk and military rank among servicemen<sup>9</sup> has been interpreted as evidence of an aetiological factor linked to affluence or social standing, insofar as all members of the military population might be presumed to have equal access to health care. A similar argument has been invoked in the interpretation of increased risks associated

**Table 3** Odds ratios (OR) and 95% CI for risks of intracranial tumors of nervous system, with respect to marital status at the time of the interview, religion, and place of birth

Characteristic	Glioma						Meningioma		Acoustic neuroma		Controls
	All glioma		High-grade		Low-grade				N	OR <sup>a</sup> (CI)	
	N	OR <sup>a</sup> (CI)	N	OR <sup>a</sup> (CI)	N	OR (CI)	N	OR <sup>a</sup> (CI)			
Marital status at time of interview											
Married <sup>b</sup>	344	1.0	255	1.0	89	1.0	139	1.0	64	1.0	454
Widowed	22	0.4 (0.2–0.7)	21	0.5 (0.3–0.8)	1	0.2 (0.0–1.2)	19	0.4 (0.2–0.8)	7	0.9 (0.3–2.4)	74
Divorced	37	0.5 (0.4–0.8)	29	0.6 (0.4–1.0)	8	0.5 (0.2–1.1)	23	0.5 (0.3–0.9)	11	1.0 (0.5–2.1)	106
Separated	10	0.6 (0.3–1.3)	7	0.7 (0.2–1.6)	3	0.6 (0.1–2.1)	4	0.3 (0.1–0.9)	0	0.0 (0.0–1.2)	26
Never married	76	0.8 (0.5–1.2)	42	1.0 (0.6–1.6)	34	0.6 (0.4–1.1)	12	0.4 (0.2–0.7)	14	1.2 (0.6–2.6)	139
Religion											
Catholic <sup>b</sup>	192	1.0	139	1.0	53	1.0	85	1.0	36	1.0	328
Protestant	191	1.0 (0.8–1.3)	141	1.0 (0.7–1.4)	50	1.1 (0.6–1.8)	64	0.9 (0.6–1.3)	40	0.8 (0.4–1.4)	319
Jewish	29	1.5 (0.8–2.7)	21	1.6 (0.8–3.2)	8	1.6 (0.6–4.2)	21	4.3 (2.0–9.0)	6	1.9 (0.6–5.3)	28
Mormon/LDS	12	1.2 (0.5–2.8)	8	1.2 (0.4–3.1)	4	1.1 (0.3–3.9)	2	0.6 (0.1–2.4)	3	0.9 (0.2–3.4)	16
Other Christian	29	0.9 (0.6–1.6)	16	0.9 (0.4–1.6)	13	1.0 (0.5–2.2)	12	1.1 (0.5–2.3)	3	0.4 (0.1–1.4)	60
None	14	1.1 (0.5–2.3)	11	2.1 (0.9–4.8)	3	0.4 (0.1–1.3)	6	1.2 (0.4–3.3)	5	1.2 (0.3–3.8)	24
Other/unknown	22	1.9 (0.9–4.1)	18	2.1 (0.9–4.9)	4	1.4 (0.3–5.9)	7	1.8 (0.6–5.5)	3	2.1 (0.3–11)	24
Place of birth											
Current state <sup>b</sup>	193	1.0	140	1.0	53	1.0	70	1.0	27	1.0	366
Adjacent state	68	1.3 (0.9–1.9)	50	1.6 (1.0–2.5)	18	0.7 (0.4–1.4)	32	1.6 (0.9–2.8)	11	0.6 (0.3–1.5)	105
Other state (USA)	187	1.3 (0.9–1.8)	132	1.4 (0.9–2.1)	55	1.1 (0.7–1.9)	72	1.2 (0.2–2.0)	55	0.9 (0.4–1.7)	290
Other country <sup>c</sup>	40	2.6 (1.5–4.6)	31	3.5 (1.8–6.5)	9	1.2 (0.5–3.0)	23	2.8 (1.4–5.6)	3	0.8 (0.2–2.7)	37

<sup>a</sup> Adjusted for matching variables, education, and self-reported household income.<sup>b</sup> Reference category.<sup>c</sup> The place of birth distribution for the 40 glioma cases was Mexico/Central America (N = 9), Canada (4), Caribbean countries (4), UK (3), Italy (3), Russia/Ukraine (3), Southeast Asia (3), France (2), Iran (2), and other (7). For the meningioma cases, the distribution was Mexico/Central America (7), China or Southeast Asia (4), former Soviet Union (3), Caribbean (2), and other European countries (6).

with white-collar occupations in Denmark, which has a national health care system accessible to all.<sup>53</sup> However, the tendency of patients to seek care, as well as the availability of care, influences diagnosis.<sup>50,54</sup>

The significantly increased OR associated with being married at the time of diagnosis for meningioma and glioma might be related to spouses noticing symptoms unapparent to their partner, encouraging their partner to seek earlier care for symptoms, influencing decisions about diagnostic examinations performed, or questioning the accuracy of physicians' diagnoses.<sup>48</sup> In the present study, the association between glioma and marital status was stronger during middle and old age than at younger ages. Symptoms such as memory loss, confusion, aphasia, and personality changes are more common in glioma patients diagnosed at older than younger ages,<sup>17</sup> and might be more noticeable to a spouse than to the affected person. The involvement of a spouse was found to be a critical determinant of the interval from onset of symptoms to final diagnosis in a consecutive series of 28 glioma patients.<sup>48</sup> Being married also has been reported to be associated with earlier stage at presentation for breast and prostate cancers.<sup>43</sup> Acoustic neuroma was not associated with marital status in the present study. Usual symptoms of acoustic neuroma (impaired hearing or balance) are quite different from those associated with glioma or meningioma.<sup>17</sup> Preston-Martin<sup>6</sup> reported higher incidence of brain tumours among married people for all age groups combined, but, between the ages of 35 and 64 years, incidence was higher among single people. Results were not presented separately for the different types of tumour.

The ratio of the number of male cases to the number of female cases was significantly higher for high-grade glioma (1.5)

than for low-grade glioma (1.0). Barker *et al.*<sup>4</sup> reported very similar results from a hospital-based survey in England. While this difference might reflect real and important differences in the aetiology or natural history of glioma in men and women, it bears mention that women in the US interact with the medical care system more often than men do, and that the disparity is not due solely to obstetric and gynaecological care.<sup>55</sup> More frequent physician visits allow greater opportunity for tumour detection and diagnosis. It is possible that, in general, a greater percentage of brain tumours are detected early in their natural history in women relative to men.

Several findings appear to be at odds with the view that delays or errors in diagnosis are largely responsible for the associations discussed above. First, a lower risk among single people than married people was seen for high-grade glioma, as well as for low-grade glioma. This is incompatible with the hypothesis as it relates to marital status, unless the diagnosis of even high-grade glioma is less than complete. Second, reported duration of symptoms prior to tumour diagnosis was not inversely associated with education or income, as might be expected if the more educated and affluent receive earlier medical care. However, as noted above, level of education might influence what a person perceives or recalls as a medically significant symptom. Third, if all low-grade gliomas eventually come to diagnosis but, for some, only after evolving to high-grade glioma, one might expect high-grade glioma to exhibit associations with education or income in the opposite direction to those seen for low-grade glioma. Our results do not show such a reciprocal pattern. It should be noted, however, that not all types of low-grade glioma tend to evolve to a higher grade, and that high-grade glioma is considerably more common than

low-grade glioma. A majority of glioblastomas appear to arise *de novo*, ('primary glioblastoma') rather than from low-grade glioma ('secondary glioblastoma').<sup>33–35</sup> Thus, one would not necessarily expect to see opposite associations of risk with education or income for high-grade glioma. Although the preceding observations do not negate a possible, or even likely, role for diagnostic delay in explaining the observed associations with education, income, insurance, and marital status, they do leave the door open to alternative explanations, including yet-to-be identified aetiological factors or, in some instances, chance.

Associations with education and income were less pronounced for meningioma than for acoustic neuroma and low-grade glioma. Some<sup>6</sup>, but not all,<sup>4</sup> previous reports have noted inverse associations between incidence of meningioma and social class. If there is an effect of socioeconomic status on probability of diagnosis of meningioma, it may be superimposed on an opposite effect due to another factor, possible aetiological, also associated with social class.

We observed evidence of an increased risk of brain tumours, particularly meningioma, among those of Jewish religion. These associations persisted after adjustment for education and income. Our results resemble those of Preston-Martin,<sup>6</sup> who noted stronger associations with Jewish religion for meningioma and acoustic neuroma than for glioma. The mortality rate due to brain cancer in New York City for the years 1953–1958 was 50–70% higher among Jews than among Protestants or Catholics.<sup>56</sup> Israel has among the highest incidence rates for cancer of the brain and nervous system in the world.<sup>57,58</sup> Future, large studies of malignant and benign brain tumours should examine joint associations with religion, family history of cancer, and environmental or lifestyle factors, to help clarify the relative contributions of environmental and genetic factors to the apparent excess incidence among Jews.

Jewish religion does not appear to explain the positive associations with foreign place of birth seen for meningioma and glioma in the present study, unlike in the study by Preston-Martin.<sup>6</sup> In a longitudinal study in the US, brain tumour mortality during 1979–1989 was significantly higher among immigrants relative to native-born people.<sup>59</sup> Neutel *et al.*<sup>60</sup> reported that the mortality rate due to brain tumours during 1970–1973 was higher among Canadians who had immigrated from the UK or western Europe than among those born in Canada or the US, but similar excesses were not observed among offspring of the immigrants. Whether this might reflect a characteristic of those self-selected for emigration, an environmental exposure associated with migration, or some other factor is unclear.<sup>60</sup> On the other hand, the incidence of cancer of the nervous system was not increased among immigrants to Sweden.<sup>61</sup> In the absence of further information, the associations with place of birth are difficult to interpret.

Hospital referral patterns might have contributed to some of the associations reported here. However, characteristics of cases and epidemiological associations with demographic factors are similar to those from population-based studies.<sup>4–6,8,57,62,63</sup> The controls included people admitted to the hospitals with a wide variety of conditions, and the observed associations with education and income generally were insensitive to the exclusion of major subgroups of controls, such as trauma patients. Furthermore, associations differed among the different types of brain tumour. This indicates that the results cannot be wholly attributable to characteristics of the control series. The case types must somehow differ from each other, either in their aetiology or in the pathways by which they came to diagnosis and treatment at the participating hospitals.

Strengths of this study include the enrolment of incident and histologically confirmed cases, high participation rates, inter-views of cases and controls under similar circumstances in the hospital, low proportions of proxy (next-of-kin) interviews, large sample size for glioma, separate evaluations for low- and high-grade glioma, and adjustment of associations with demographic variables for possible confounding variables. Limitations include small sample size for less-common tumour types and an inability to isolate factors responsible for the observed associations.

In summary, intracranial tumours of the brain and nervous system comprise a clinically, biologically, and, most probably, aetiotogically heterogeneous group. Considerable heterogeneity exists even between low-grade and high-grade gliomas. Existing data are insufficient to discriminate between hypotheses related to tumour aetiology and those related to tumour diagnosis, and the alternatives are not mutually exclusive. However, the findings with respect to education, income, health insurance coverage, and marital status lend support to the view that these associations may relate more to the diagnosis of tumours than to their inception. If true, this would imply that tumours are not being diagnosed in certain subgroups of the population as early as they might be, and not just for histologically benign tumours. If earlier diagnosis would allow for more effective treatment of clinically significant tumours, such a delay would be of medical importance. Slow-growing tumours also pose challenges for aetiological studies, both because of possible intrapopulation differences in the completeness of diagnosis, and because the relevant exposure periods are likely to be many years prior to diagnosis.

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## KEY MESSAGES

- In a hospital-based case-control study conducted in the US, associations with sociodemographic indicators varied considerably among high-grade glioma, low-grade glioma, meningioma, and acoustic neuroma.
- Incidence was positively associated with indicators of affluence (income, education, type of health coverage) for slow-growing tumours, but not for the more rapidly growing high-grade gliomas.
- The risk of meningioma and glioma, but not acoustic neuroma, appeared to be increased among those *currently* married relative to currently unmarried people (regardless of previous marital history).
- The basis of the associations with social class and marital status remains unknown, but delayed or incomplete diagnosis among people of lower social standing and those not living with a partner might play a role.
- An increased risk of meningioma associated with Jewish religion was observed that could not be explained by education or income.

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